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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,143	11/17/2003	Rajiv Shah	047711-0325	1899
23392 7590 08/07/2008				
FOLEY & LARDNER				
2029 CENTURY PARK EAST				
SUITE 3500				
LOS ANGELES, CA 90067				
EXAMINER				
PAK, YONG D				
ART UNIT		PAPER NUMBER		
1652				
MAIL DATE		DELIVERY MODE		
08/07/2008		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/715,143

Applicant(s)

SHAH ET AL.

Examiner

Yong D. Pak

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 April 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) 18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-17 and 19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/CDC)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date _____

DETAILED ACTION

The amendment filed on April 8, 2008, adding claim 19, has been entered. No new matter has been entered.

Claims 1-19 are pending. Claim 18 is withdrawn. Claims 1-17 and 19 are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on April 8, 2008, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112 – 2nd paragraph

In view of applicant's argument, the rejection of claims 7-10 and claims 11-18 depending therefrom under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been **withdrawn**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 7-14, 17, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al., Cherry et al. and Hatzinikolaou et al.

Claims 1-3, 7-14, 17, and 19 are drawn to a method of formulating glucose oxidases by obtaining an organism, such as an *E. coli*, with glucose oxidase genes, growing colonies of the organism, altering the environment of the colonies, such as introducing peroxide, screening the colonies to identify colonies with active glucose oxidase for a predefined, desired functionality, such as use in glucose sensors, and determining whether the colonies grown in the presence of peroxide are active.

Valdes et al. (cited previously on form PTO-892) discloses that glucose oxidase in glucose sensors are degraded by peroxide and this "decay can lead to the eventual failure of the sensor" (abstract and page 367). Valdes et al. teaches that to ensure longer sensor functionality, instead of replacing the sensor with fresh enzyme, as has been practiced in the art, techniques to "prevent the degradation of the enzyme" is advantageous (page 375). With this teaching at hand, one having ordinary skill in the art would conclude that glucose oxidase may be prevented by using chemical agents, as suggested by Valdes et al. or to use glucose oxidase mutants that are resistant to peroxide since methods of generating mutants having resistance to chemicals are known in the art, as discussed below. Valdes et al. also teaches a method of determining activity of glucose oxidase (page 370).

The difference between the reference of Valdes et al. and the instant invention is that the reference of Valdes et al. does not teach a method of producing mutant glucose oxidase that is resistant to degradation from peroxide. However, there are many methods widely available in the art of creating mutant genes by random mutations and screening for mutants displaying desired functional properties, such as having resistance to a chemical, such as a peroxide.

Cherry et al. (Nat Biotechnol. 1999 Apr;17(4):379-84 - form PTO-892) discloses a method of making mutants of an enzyme which is also degraded in the presence of hydrogen peroxide by using directed evolution techniques, both DNA shuffling and error prone PCR (abstract). Cherry et al. discloses that after multiple rounds of directed evolution an enzyme, mutants of said enzyme that are resistant to deactivation in the

presence of high concentration of hydrogen peroxide, conditions that mimic of hydrogen peroxide wherein the enzyme is normally deactivated, were obtained (pages 380-382). Cherry et al. discloses that colonies having enzymatic activity were selected to determine for its resistance against hydrogen peroxide (page 382).

Hatzinikolaou et al. (cited previously on form PTO-892) discloses a library of glucose oxidase genes known in the art, such as *A. Niger* (page 371). Hatzinikolaou et al. also discloses a method of isolating and purifying glucose oxidase as recited in claims 10-14 and 17 and methods of measuring glucose oxidase activity and concentration of glucose oxidase (pages 372-373).

Therefore, combining the teachings of Valdes et al., Cherry et al. and Hatzinikolaou et al., it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to apply the method of Cherry et al. to formulate or produce mutant glucose oxidases having resistance to peroxide by generating a library of mutated genes using the glucose oxidase gene of Hatzinikolaou et al., transforming *E. coli* with vectors comprising each of the mutated genes, growing colonies of said cells and determining whether the colonies have active glucose oxidase followed by determining whether the colonies or the glucose oxidase comprised in the colony are resistant to peroxide and then test for the functionality of the glucose oxidase in a glucose sensor. One of ordinary skill in the art would have been motivated to produce mutant peroxide resistant glucose oxidases in order to use them in glucose sensors, thereby prolonging their use, since Valdes et al. teaches that glucose oxidases in glucose sensors are degraded by peroxide, leading to failure of the sensor. One of

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ordinary skill in the art would have had a reasonable expectation of success since Hatzinikolaou et al. teaches glucose oxidase genes and Cherry et al. teaches a comparable method of generating a library of mutant having resistance to hydrogen peroxide. Therefore, using the known technique of Cherry et al. to generate mutants of an enzyme having resistance against hydrogen peroxide would have been obvious to one of ordinary skill in the art.

Therefore, the above references render claims 1-3, 7-14, 17, and 19 *prima facie* obvious.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the prior art of record does not teach or suggest the claimed invention because (1) Valdes et al. show that the direction taken by those skilled in the art was away from the method of the presently claimed invention; and (2) neither Cherry et al. and Hatzinikolaou et al. teach formulating glucose oxidase enzyme by obtaining an organism with a glucose oxidase gene and screening colonies to identify colonies with active glucose oxidase (those that are resistant to peroxide degradation) after altering the environment of colonies. Examiner respectfully disagrees.

(1) While it is true that Valdes et al. do not teach a method of producing a library of mutated glucose oxidase genes, Valdes et al. does teach that another option of addressing the peroxide degradation of glucose oxidase is to "prevent the degradation of the enzyme using other chemical agents or, techniques" (page 375, left paragraph).

Contrary to applicant's argument that that the Examiner has quoted the above statement out of context to imply that Valdes et al. would have suggested a process involving creating mutated genes of glucose oxidase as claimed in the instant claims, Examiner is taking the position that one having ordinary skill in the art would have concluded that peroxide degradation of glucose oxidase may be prevented by using chemical agents, as suggested by Valdes et al. or to use other "techniques", generating glucose oxidase mutants that are resistant to peroxide since methods of generating mutants having resistance to chemicals are known in the art, as taught by Cherry et al. Applicants also points out that Valdes et al. immediately follows the above statement with a description of the use of chemical additives as the so-called "better options" and therefore Valdes et al. teach a specific direction (use of chemical additives) that departs from the conventional process of replacing a degraded enzyme with a fresh enzyme. However, the absence of alternatives of a solution (i.e. mutant glucose oxidase resistant to peroxide degradation) does not criticize, discredit, or otherwise discourage the solution claimed. Since Valdes et al. does not teach that mutant glucose oxidase resistant to peroxide degradation is "undesirable", Valdes et al. does not teach away from the claimed method. See MPEP 2145, section D and *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

(2) In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir.

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1986). The reference of Cherry et al. is relied upon for its teaching of a method of making mutants of an enzyme which is also degraded in the presence of hydrogen peroxide by using directed evolution techniques, both DNA shuffling and error prone PCR (abstract). The reference of Hatzinikolaou et al. is relied upon for its teaching of several glucose oxidase genes known in the art, such as *A. Niger* (page 371), from which a library of mutant glucose oxidase genes can be obtained by using the method of Cherry et al., and a method of isolating and purifying glucose oxidase as recited in claims 14-18 and methods of measuring glucose oxidase activity and concentration of glucose oxidase (pages 372-373).

Applicants also argue that the rejection is improper because prior art provides no motivation to combine and teaches away from the combination suggested by the Examiner because (1) Valdes et al. and other prior art teaches away from the claimed method; (2) none of the cited prior art provide motivation to combine; and (3) without the present disclosure as a guide, one of ordinary skill in the art would not have arrived at the claimed invention. Examiner respectfully disagrees.

(1) As discussed above, Valdes et al. does teach that another option of addressing the peroxide degradation of glucose oxidase is to “prevent the degradation of the enzyme using other chemical agents or, techniques” (page 375, left paragraph). With this teaching at hand, one having ordinary skill in the art would have concluded that peroxide degradation of glucose oxidase may be prevented by using chemical agents, as suggested by Valdes et al. or to use other “techniques” known in the art,

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such as generating glucose oxidase mutants that are resistant to peroxide since methods of generating mutants having resistance to chemicals are known in the art, as taught by Cherry et al. Valdes et al. does not teach away from a method of formulating glucose oxidase enzyme by obtaining an organism with a glucose oxidase gene and screening colonies to identify colonies with active glucose oxidase (those that are resistant to peroxide degradation) after altering the environment of colonies because the absence of alternatives of a solution (i.e. mutant glucose oxidase resistant to peroxide degradation) does not criticize, discredit, or otherwise discourage the solution claimed. Since Valdes et al. does not teach that mutant glucose oxidase resistant to peroxide degradation is "undesirable", Valdes et al. does not teach away from the claimed method. See MPEP 2145, section D and *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

(2) "[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw there from." (MPEP 2144). The rationale to modify or combine the prior art does not have to be expressly stated in the prior art and the strongest rationale for combining references is a recognition, drawn from a convincing line of reasoning that some advantage would have been produced by their combination. In the instant case, since Valdes et al. teaches that glucose oxidases in glucose sensors are degraded by peroxide, leading to failure of the sensor, and methods of making mutant enzymes with desirable properties was known in the art (Cherry et al),

one having ordinary skill in the art would have been motivated to combine the cited references in order to produce mutant peroxide resistant glucose oxidases in order to use them in glucose sensors, thereby prolonging their use.

(3) It appears that applicant's are arguing that the examiner's conclusion of obviousness is based upon improper hindsight reasoning derived from applicant's specification. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, prior art teaches that glucose oxidase is degraded by hydrogen peroxide (Valdes et al.) and teaches that this problem can be addressed by preventing degradation of the enzyme. Cherry et al. teaches a method of making mutant enzymes enzyme having an advantageous predetermined property, such as resistance to a chemical, knowledge which was within the level of ordinary skill. Therefore, the motivation to combine the cited reference are not derived from applicant's own specification, but the motivation comes from the combined teachings of the cited references.

Applicants also argue that each of the dependent claims 2, 3, 1-14, and 17 recite further features that distinguish those claims from the prior art. The instant rejection is

not an anticipatory rejection. "[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw there from." (MPEP 2144). Regarding claim 1, Hatzinikolaou et al. discloses *A. niger* with a glucose oxidase gene and several glucose oxidase genes that have been cloned, which one of ordinary skill in the art can express in *E. coli*. It would have been obvious to one having ordinary skill in the art to alter the environment of the colonies by introducing peroxide, test colonies with active glucose oxidase, continue to alter the environment of the colonies as recited in claims 3, 7, and 8 since Cherry et al. discloses a method of generating a library of mutant genes and screening for clones/colonies having the desired property. It would have been obvious to one having ordinary skill in the art to test glucose oxidase as recited in claim 9 since Wagner et al. discloses a method of determining glucose oxidase activity via a sensor. It would have been obvious to one having ordinary skill in the art to isolate glucose oxidase as recited in claims 10-14, and 17 since such isolation techniques are taught by Cherry et al. and Hatzinilolaou et al.

Claims 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al., Cherry et al. and Hatzinikolaou et al. as applied to claims, 1-3, 7-14 and 17 above, and further in view of MIXONIX.

Claims 15-16 are drawn to a method of formulating or producing mutant glucose oxidases, wherein colonies comprising said mutant glucose oxidase is disrupted via sonication.

Valdes et al., Cherry et al. and Hatzinikolaou et al. in combination teaches a method of formulating or producing mutant glucose oxidases, as discussed above.

The difference between the reference of Valdes et al., Cherry et al. and Hatzinikolaou et al. and the instant invention is that said references do not teach a method of disrupting cells via sonication.

However, disrupting cells via sonication, through the use of a sonicator, during protein purification is well known and routinely practiced in the art, see MISONIX (form PTO-892).

Therefore, combining the teachings of Valdes et al., Cherry et al. and Hatzinikolaou et al. and MISONIX, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to disrupt cells comprising mutant glucose oxidase via sonication. One of ordinary skill in the art would have been motivated to do so in order to disrupt cells comprising the mutant glucose oxidase. One of ordinary skill in the art would have had a reasonable expectation of success since disruption of cells using sonication is well known and practiced routinely in the art.

Therefore, the above references render claims 15-16 *prima facie* obvious.

In response to the previous Office Action, applicants have traversed the above rejection for reasons discussed above.

Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al., Cherry et al. and Hatzinikolaou et al. as applied to claims 1-3, 7-14 and 17 above, and further in view of Wagner and Aldrich Catalog.

Claims 4-6 are drawn to a method of formulating or producing mutant glucose oxidases by obtaining a library of glucose oxidase genes, creating a library of mutated glucose oxidase genes, introducing each mutated glucose oxidase genes into separate expression vectors, inserting said vectors into host organisms, growing colonies of the host organism, determining whether the colonies contain active glucose oxidase by testing glucose oxidase in sensors and using fluorescence of a leuco-cryalsta-violet, and determining whether the colonies are resistant to peroxide.

Valdes et al., Cherry et al. and Hatzinikolaou et al. in combination teaches a method of formulating or producing mutant glucose oxidases, as discussed above.

The difference between the reference of Valdes et al., Cherry et al. and Hatzinikolaou et al. and the instant invention is that said references do not teach a method of determining whether the colonies contain active glucose oxidase by testing glucose oxidase in sensors and using fluorescence.

Wagner (EP 0 251 475 A1 – cited previously on form PTO-892) discloses a method of determining glucose oxidase activity via a sensor by measuring fluorescence emission from a dye, wherein oxidation of glucose by active glucose oxidase reduces the fluorescence emission (pages 2-3). In the method of Wagner, the glucose oxidase is conjugated to a dye and immobilized in the sensor (page 3). Wagner also teaches that any fluorescent dye sensitive to quenching of its fluorescence emission by oxygen

can be used (page 5). Aldrich Catalog (cited previously on form PTO-892) discloses a leuco-cryalsta-violet dye (page 1005).

Therefore, combining the teachings of Valdes et al., Cherry et al. and Hatzinikolaou et al., Wagner and Aldrich Catalog, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use the method of Wagner to ascertain activity of the glucose oxidase, wherein glucose oxidase is isolated and purified by the method taught by Hatzinikolaou et al. One of ordinary skill in the art would have been motivated to do so in order to determine whether the colonies comprising mutated glucose oxidases have active glucose oxidase. One of ordinary skill in the art would have had a reasonable expectation of success since Wagner teaches how to determine activity of glucose oxidase by measuring fluorescence emission from a dye, wherein oxidation of glucose by active glucose oxidase reduces the fluorescence emission.

Therefore, the above references render claims 4-6 *prima facie* obvious.

In response to the previous Office Action, applicants have traversed the above rejection for reasons discussed above. Further applicants argue that neither Wagner nor Aldrich Catalog would lead to the presently claimed invention since neither of the references teach or suggest formulating a glucose oxidase enzyme by mutating glucose oxidase to make them resistant to peroxide degradation. However, the motivation to combine the cited references is to produce mutant peroxide resistant glucose oxidases in order to use them in glucose sensors, thereby prolonging their use, since Valdes et al. teaches that glucose oxidases in glucose sensors are degraded by peroxide, leading

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to failure of the sensor, and Cherry et al. teaches a method of producing mutant enzymes that are resistant to peroxide degradation.

Hence the rejection is maintained.

Conclusion

None of the claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Yong D Pak/
Primary Examiner, Art Unit 1652